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Semantic Memory Impairment in the Earliest Phases of Alzheimer's Disease

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Key Words
Alzheimer's disease · Semantic memory · Neuropsychology · Mild cognitive impairment

Abstract
The presence and the nature of semantic memory dysfunction in Alzheimer's disease (AD) have been widely debated. This study aimed to determine the frequency of impaired semantic test performances in mild AD and to study whether incipient semantic impairments could be identified in predementia AD. Five short neuropsychological tests sensitive to semantic memory and easily applicable in routine practice were administered to 102 patients with mild AD (Mini-Mental State Examination score above 19), 22 predementia AD patients and 58 healthy subjects. 'Category fluency' and 'naming of famous faces' were the most frequently impaired tests in both patient groups. The study demonstrated that impairments on semantically related tests are common in mild AD and may exist prior to the clinical diagnosis. The results imply that assessment of semantic memory is relevant in the evaluation of patients with suspected AD.

Introduction

The hallmark of Alzheimer's disease (AD) is a marked impairment in episodic memory, which may exist years before a clinical diagnosis of dementia can be established [1, 2]. Semantic memory has theoretically been distinguished from episodic memory and concerns knowledge of facts, words, objects and their meaning. It is culturally shared and is not time dependent [3]. Impairments in semantic memory can be found on tests of naming of objects [4] as well as naming and recognition of faces of famous people [5, 6]. Subtests of the Wechsler Adult Intelligence Scale battery also tap semantic memory. Further, AD patients are typically more impaired on category than on phonological fluency tasks [7–9], indicating a semantic impairment.

Tests of semantic functions may be helpful to an earlier and more efficient assessment of AD [10], but the number of studies on clinical presentation of semantic memory dysfunction in AD are limited. Studies have addressed the presence of semantic memory impairments [11], typically by group comparisons of AD patients and healthy controls. However, few studies have reported how frequent semantic impairments are. One study found semantic impairments in about 50% of patients with mild

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AD [12]. Importantly, semantic memory (together with spatial functions) may be the most important cognitive domain for the performance of everyday skills [12].

Only few studies have described if impairments on semantically related tasks could be identified in patients with AD prior to the diagnosis of dementia, but some studies indicate that such subtle impairments can be found [13–15]. In general, these studies did not specifically assess semantic functions, and whether semantic memory deficits exist in addition to episodic memory impairment in the prodromal phase of AD has not been extensively studied.

This descriptive study aimed to investigate the frequency of semantic impairments in mild AD. Further, we wished to study to which extent incipient semantic memory impairment may be present in patients with predementia AD.

Methods

Subjects

In this study, we included 102 patients with mild AD and 22 with predementia AD. The patients all participated in a prospective research program on questionable or mild dementia and were recruited consecutively from referrals to the Copenhagen University Hospital Memory Clinic. The research program consecutively included all referred patients, aged 60 years or above, with Mini-Mental State Examination (MMSE) scores greater than or equal to 20. The clinical assessment program included an examination by a neurologist who conducted a physical and neurological examination (including testing with MMSE). Blood tests were also performed at the initial visit. The neurologist determined the indications for further investigations in collaboration with other specialists [16]. In addition to routine clinical assessment, all patients had an MRI or a CT scan and a neuropsychological assessment with the Danish Mental Status Test (DMST; see below). Further relevant investigations, e.g. single photon emission computed tomography, psychiatric evaluation or electroencephalography were performed when clinically indicated. After the assessments had been completed, a consensus diagnosis was established according to international diagnostic criteria.

Inclusion Criteria for Mild AD

All patients from the prospective research program meeting the NINCDS-ADRDA criteria [17] for probable AD and criteria for dementia by DSM-IV [18].

Inclusion Criteria for Predementia AD Patients

All patients from the prospective research program meeting the following criteria: (1) criteria for mild cognitive impairment (MCI), and (2) documentation for later progression to AD as determined from annual reassessments (mean progression time from the baseline visit was 17 months, SD 5.6, range 10–30). Progression from MCI to AD was operationalized as a decline in functional abilities resulting in impairments in everyday activities together with progression of episodic memory impairment and decline in any other cognitive domain (attention, abstraction, language, visual perception and visuoconstruction). MCI was defined by an operationalization of the criteria by Petersen et al. [19]. These criteria were: (1) complaints of cognitive dysfunction either from the patient or by an informant; (2) a cognitive profile on neuropsychological testing with a domain z score on memory below –2 SD and other domain scores above –2 SD on age- and education-corrected norms; (3) a score on the Clinical Dementia Rating of 0.5; (4) intact activities of daily living functioning by clinical judgement, and (5) no dementia (patients did not meet the NINCDS-ADRDA criteria [17] for probable AD or DSM-IV criteria for dementia [18] since their daily functional abilities were unimpaired and their cognitive deficits were too mild or equivocal for a diagnosis of AD).

Importantly, patients with any known or suspected cause for memory impairment, e.g. alcohol abuse, anxiety disorder or depression, were not classified as having MCI in order to include only 'amnesic' MCI patients (as described by Petersen et al. [19]).

By the end of the inclusion period, 22 of 30 MCI patients had progressed to AD, and these patients were included in the predementia AD group.

Healthy Control Subjects

The control group for this study consisted of 58 healthy elderly volunteers. They were selected from a cohort of 102 healthy persons to match the 2 patient groups on age and education. Recruitment of the healthy controls was done by newspaper advertisement. Persons with a history of alcohol or drug abuse, severe psychiatric illness, neurological disease and other interfering handicaps (e.g. hearing problems) were excluded.

Demographic characteristics of the patient groups and the healthy controls can be found in table 1.

Neuropsychological Assessment

The DMST is a Danish test battery containing 28 subtests, most of which are modifications of internationally well-known cognitive tests [20]. The test battery consists of a quantitative version of the Mental Status Examination [21] and additional tests for memory (e.g. famous persons), attention (Stroop modified), abstraction (picture arrangement), visuoconstruction (e.g. block design) and perception (Street Completion Test and Poppelreuter Overlapping Figures). For diagnostic classification, the tests were grouped in 6 cognitive domains: memory, attention, abstraction, language, visual perception and visuoconstruction according to the procedure described by Waldemar et al. [20]. Based on the control material in Waldemar et al. [20], a computerized method correcting for age and education for calculating composite domain z scores was developed and used to evaluate performances in the 6 cognitive domains.

Assessment of Semantic Memory

We selected 5 tests from the DMST with semantic properties for assessing semantic functions. They are all short, simple to administer and are well tolerated by patients. All tests are internationally known. The following tests were used. (1) *Category fluency* (animals). One minute allowed. (2) *Naming* of 30 colored line drawings of common objects in 6 categories. (3) *Famous faces* using 20 photographs of nationally and internationally famous public persons. All have been famous for at least 15 years. (a) *Naming:* the patient is first asked to give the name of the person presented on the photograph. One point is given for each correct answer. Scores 0–20. (b) *Identification:* with correct naming, an identification score of 1 was applied immediately.

Table 1. Demographic and clinical data

	Females/ males	Age	Education years	MMSE score
Controls (n = 58)	30/28	74.1 (4.9) range 64–84	11.6 (2.8)	29.2 (0.88) range 27–30
Predementia AD (n = 22)	13/9	75.8 (4.4) range 66–84	11.1 (2.9)	26.0 (1.95)[1] range 22–29
Mild AD (n = 102)	65/37	75.9 (6.1) range 62–87	11.4 (2.8)	24.0 (2.48)[2] range 20–30

MMSE was only applied to 45 controls. Figures are means, with SD in parentheses.
[1] Significantly different from controls ($p < 0.05$; Mann-Whitney U test).
[2] Significantly different from predementia AD and controls ($p < 0.05$; Mann-Whitney U test).

Table 2. Frequency of impairment (percentages) for patients and healthy controls in the 6 cognitive domains

	Memory impaired	Attention impaired	Abstraction impaired	Language impaired	Perception impaired	Construction impaired
Controls (n = 58)	0	0	0	0	0	0
Predementia AD (n = 22)	100	0	0	0	0	0
Mild AD (n = 102)	100	31	30	44	30	27

Impairment was defined as a domain z score < –2.0.

When naming failed, the patient was asked to give important details of the person such as nationality, employment, or why the person is famous (e.g. J.F. Kennedy 'president who was shot'). This was done to assess whether knowledge about the person could be elicited. With correct description, a score of 1 was applied. Scores 0–20. (4) *Information:* answering 7 questions of common knowledge (e.g. 'What is the capital of Spain?', 'Who wrote *The Ugly Duckling*?').

Data Analysis

For the 58 healthy control subjects, normally distributed scores on the semantic tests were only found for 'category fluency'. For this test, scores below –2 SD were considered indicative of a significant impairment. The remaining 4 semantic tests had skewed distributions of scores with ceiling effects in the control group. We defined the cutoff scores for these 4 tests by an approximation to scores below –2 SD. We tried to avoid false-positives by defining the cutoff as the lowest score for each test that classified no more than 1 person of the control population as impaired.

A disproportionate relationship between category and phonological fluency may indicate that semantic properties of the test are impaired. Thus, we also assessed the number of impaired mild and predementia AD patients on 'phonological fluency' (s-words). For this test, performances below –2 SD were considered indicative of a significant impairment.

In the analysis of differences between the three groups, we used one-way analysis of variance (ANOVA) when normal distribution and equal variances could be assumed. For the comparison of MMSE scores between the groups, Mann-Whitney U tests were performed. Since 4 out of 5 semantic tests had skewed distributions with ceiling effects, the Mann-Whitney U test was also used to assess differences in test scores between the groups. For the group comparisons of domain scores, Student t tests were applied. We used the χ^2 test to examine differences in percentage of patients classified as impaired in the mild and the predementia AD groups, and Fischer's exact test (two-sided) was applied when cells had expected counts of less than 5. To establish a composite score for the degree of semantic dysfunction, we computed the number of tests that were impaired for each patient leading to a continuous measure for semantic impairment (scores 0–5).

Results

Demographic data for the three groups and MMSE scores are presented in table 1. One-way ANOVA followed by Bonferroni-corrected t tests showed no significant differences between any of the three groups concerning age or education. MMSE scores differed significantly between all groups, although scores were overlapping. In table 2, the frequencies of patients classified as significantly impaired in the 6 cognitive domains are shown.

Table 3. Performances of the three groups on the 5 semantic tests

	Mild AD (n = 102)	Predementia AD (n = 22)	Control (n = 58)
Category fluency	10 (4–22)[1,2]	13 (9–22)[1]	21.5 (13–32)
Identification of famous persons	16 (3–20)[1,2]	18 (12–20)[1]	20 (13–20)
Naming of famous persons	10 (1–20)[1,2]	15 (12–20)[1]	19 (11–20)
Information	5 (0–7)[1]	5 (1–7)[1]	7 (4–7)
Naming	29 (15–30)[1,2]	30 (29–30)	30 (20–30)

Figures are median, with ranges in parentheses.
[1] Significantly different from controls ($p < 0.05$; Mann-Whitney U test).
[2] Significantly different from predementia AD ($p < 0.05$; Mann-Whitney U test).

Mild AD patients were significantly more impaired in all domains (except memory) than the predementia AD patients.

Results from the semantic tests in the two groups of patients and in the controls are summarized in table 3. When comparing differences in test performances on a group basis, we found that the mild AD group was significantly impaired compared with the control group on all semantic tests. Test performances in the predementia AD group compared to healthy controls were significantly lower in 4 out of the 5 semantic tests: 'category fluency' ($z = -5.537$, $p < 0.001$), 'identification of famous faces' ($z = -4.561$, $p < 0.001$), 'naming of famous faces' ($z = -5.439$, $p < 0.001$), and 'information' ($z = -5.287$, $p < 0.001$). For 'category fluency' ($z = -3.513$, $p < 0.001$), 'identification of famous faces' ($z = -2.403$, $p = 0.016$), 'naming of famous faces' ($z = -2.752$, $p = 0.006$), and 'naming' ($z = -2.770$, $p = 0.006$) significant differences were found between performances of the predementia AD and mild AD groups. Thus, at a group level, all measures of semantic memory were impaired in mild AD, and impairments could be found even in predementia AD.

All patients' individual profiles on the semantic tests were assessed to evaluate the frequency of impairment on each test (table 4). 'Category fluency' followed by 'naming of famous faces' were the tests most commonly below normal range. 'Naming' classified only 14.9% as significantly impaired in the AD group and none in the MCI group. For all 5 tests, the percentage of impaired patients was higher in the AD group, but significant differences between the percentage of impaired patients in the two patient groups were not found for 'naming' ($p = 0.071$) using Fischer's exact test. In 'phonological fluency' (s-words), none were impaired in the predementia AD group, and 14% of the mild AD patients were significantly impaired on this test.

Table 4. Frequency of impaired semantic test performances in the two AD groups

	Mild AD (n = 102)	Predementia AD (n = 22)
Category fluency	64 (62.7)[1]	7 (31.8)
Naming of famous persons	54 (53.5)[1]	5 (22.7)
Information	50 (49.5)[1]	5 (22.7)
Identification of famous persons	39 (38.6)[1]	3 (13.6)
Naming	15 (14.9)	0 (0)

Figures are numbers, with percentages in parentheses.
[1] Significant difference (χ^2 test; two-tailed; $p < 0.05$) in the percentage of patients being classified as impaired as compared to predementia AD.

The number of significantly impaired tests was computed for each patient giving a composite measure for semantic reduction (scores 0–5). The results are presented in table 5. Eighteen percent of the patients with mild AD had no impairment on semantic tasks. Among mild AD patients, the majority had mild or moderate semantic impairment, and 24.5% had severe semantic dysfunction as indicated by impairment in 4 or 5 tests. For predementia AD patients, 59% had 1 or more test performances below the expected range, but only 9% were impaired on 3 or 4 tests. These results show that semantic memory impairments are very frequent and may be prominent in mild AD. Minor impairments are found in predementia AD although subtle in degree.

Table 5. Number of impaired semantic tests (out of 5) in predementia and mild AD

Impaired tests	Predementia AD (n = 22)	Mild AD (n = 102)
0	9 (41.0)	18 (17.6)
1	10 (45.5)	22 (21.6)
2	1 (4.5)	17 (16.7)
3	1 (4.5)	20 (19.6)
4	1 (4.5)	19 (18.6)
5	0	6 (5.9)

Figures are numbers, with percentages in parentheses.

Discussion

Although patients with AD often are impaired on tests of semantic memory [22], the presence of semantic dysfunction in AD has been widely debated. While some studies have concluded that AD leads to loss of semantic knowledge [11, 23], others have indicated that the primary deficit is one of decreased access with no reduction in the semantic memory per se [24, 25]. The lack of consensus may be caused by different methodological approaches and differences in the level of assessment [26].

In the present study, we explored the use of short tests with a semantic content, all easily applicable in clinical practice in terms of patient acceptance and time. Compared to previous reports, this study not only describes group differences between AD patients and controls, but information is also provided on how frequently semantic disturbances occur. Almost all patients with mild AD had some degree of impaired performance on these tests. Our results showed that deficits on semantic tests are common in early AD, demonstrating that semantic memory is likely to be among the first impaired cognitive functions as previously described [15, 22]. Importantly, our results showed a wide variability between patients concerning which tests were significantly impaired supporting previous findings of individual variations in semantic dysfunction [27].

A second objective of our study was to assess if deficits in selected semantic tests could be found in patients with predementia AD prior to the diagnosis of AD. At the group level, predementia AD patients had significant impairments compared to controls on 4 out of 5 semantic tests, but when we assessed the frequency of test performances below the cutoff scores, 86% had 0 or 1 test impaired only. Thus, changes in semantic memory can be found in predementia AD patients, but only subtle in degree. Our study resembles the findings from a small longitudinal study with 12 patients where semantic deficits could also be identified prior to a diagnosis of AD [15].

The high frequency of semantic dysfunction in the earliest stages of AD has important clinical implications. First, semantic memory tests may be sensitive diagnostic tests in the assessment of patients suspected to have dementia (for a recent review, see Spaan et al. [10]). The tests described here are all short and easy to use in everyday clinical assessment. More sensitive and 'pure' semantic batteries exist (e.g. Hodges et al. [11]), but they are time-consuming and more difficult to implement in routine clinical practice. Further, tests for semantic memory have been found to correlate strongly with patients' functional performance [12]. This correlation highlights that assessment of semantic memory is important in early AD when trying to identify patients in need of professional assistance and care.

Our data are representative for a subgroup of all MCI patients, and whether semantic impairments are present in MCI patients in general cannot be addressed with our data. This study was not intended to assess whether deficits in semantic memory are predictive for AD. This question cannot be addressed with our data, since all included predementia AD patients later progressed to AD. The predementia AD patients came from a larger group of amnesic MCI patients, but comparisons of patients who progressed to AD and nonconverting patients were not meaningful, since follow-up time for some of the patients who did not progress to AD was shorter than for the predementia AD patients. Other studies have investigated markers for progression from MCI to AD, and semantic memory tests have been found to be predictive in some papers [13, 14], although not in others [28, 29]. In a recent large study, 'category fluency' was significantly impaired in 'questionable dementia' patients compared to controls [30]. Since our data demonstrated that subtle changes in semantic memory may be present prior to the clinical diagnosis of dementia in some patients who develop AD, the use of semantic measures may be relevant in future studies on markers for progression from MCI to AD.

Semantic deficits may be caused by damage to the temporal cortex. This has been indicated in AD [31] and in disorders with isolated semantic impairment, e.g. semantic dementia [32] and herpes simplex encephalitis [33, 34]. In an early stage of AD, neurofibrillary tangles can be found in the temporal neocortex [35]. This may explain the clinical manifestation of semantic impairments even prior to the diagnosis of AD and the high frequency of

semantic memory impairment found in our mild AD group.

Some tests were more frequently impaired than others. Performances on 'category fluency' and 'naming of famous faces' were most frequently below the cutoff scores. 'Category fluency' has been described as a sensitive test for semantic impairment [22], although impaired verbal fluency could result from psychomotor slowing, poor use of strategy and other deficits not related to semantic functions. Our results showed a significant difference in the frequency of impairment between 'phonological fluency' and 'category fluency', which is generally assumed to reflect the presence of a semantic dysfunction [9].

As in previous studies [6], performances on 'identification of famous faces' and 'naming of famous faces' were frequently impaired, which we suggest may be caused by the vulnerability of the unique features of persons. Impairment of naming is one of the core symptoms of semantic deterioration in AD [4], but our data showed that a simple naming test with only common objects (e.g. cat, bicycle, shoe) had the lowest frequency of impairment of the semantic tests, classifying only 15% in the mild AD group as significantly impaired. Hodges and Patterson [22] found that more than 50% fell below the normal range in a similar patient group on the picture naming test from their semantic battery. Our results imply that more comprehensive naming tests, i.e. with graded difficulty, should be preferred in the assessment of mild AD. 'Graded naming test' has been found to be sensitive in the earliest phases of AD [6].

A possible limitation of our study was that the semantic test scores contributed to the diagnosis of dementia because patients with significant impairment in cognitive domains other than episodic memory were by definition classified as meeting clinical criteria for dementia. However, in the mild AD group, the composite domain score in language (where semantic tests were categorized) was not disproportionally impaired compared to attention, abstraction, perception and visuoconstruction. Further, we used conservative cutoff scores to avoid false-positive diagnosis. We therefore assume that the frequency of semantic impairments in this population is representative of what is normally found in AD. Since performances on the semantic tests contributed to the diagnostic classification of the patients, conclusions regarding group differences between predementia AD and mild AD cannot be made. However, such group comparisons were not the objective of this study, since our interest was to assess the frequency of semantic memory impairments in different stages of AD as compared to healthy controls.

In conclusion, our results demonstrate that semantic memory impairments are common in the earliest phases of AD although individual differences exist. Even in predementia AD, subtle semantic impairments can be detected at a group level, and in mild AD, semantic memory disturbances may be prominent. The results imply that assessment of semantic functions should be central in the neuropsychological testing of suspected AD. The study also demonstrates that short tests with a semantic content are sensitive to impairments in the earliest phases of AD. Such tests can easily be implemented in everyday clinical practice.

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References

1 Linn RT, Wolf PA, Bachman DL, Knoefel JE, Cobb JL, Belanger AJ, Kaplan EF, D'Agostino RB: The 'preclinical phase' of probable Alzheimer's disease. A 13-year prospective study of the Framingham cohort. Arch Neurol 1995; 52:485–490.

2 Masur DM, Sliwinski M, Lipton RB, Blau AD, Crystal HA: Neuropsychological prediction of dementia and the absence of dementia in healthy elderly persons. Neurology 1994;44: 1427–1432.

3 Tulving E: Elements of Episodic Memory. New York, Oxford University Press, 1983.

4 Martin A, Fedio P: Word production and comprehension in Alzheimer's disease: The breakdown of semantic knowledge. Brain Lang 1983; 19:124–141.

5 Hodges JR, Salmon DP, Butters N: Recognition and naming of famous faces in Alzheimer's disease: A cognitive analysis. Neuropsychologia 1993;31:775–788.

6 Thompson SA, Graham KS, Patterson K, Sahakian BJ, Hodges JR: Is knowledge of famous people disproportionately impaired in patients with early and questionable Alzheimer's disease? Neuropsychology 2002;16:344–358.

7 Butters N, Granholm E, Salmon DP, Grant I, Wolfe J: Episodic and semantic memory: A comparison of amnesic and demented patients. J Clin Exp Neuropsychol 1987;9:479–497.

8 Cerhan JH, Ivnik RJ, Smith GE, Tangalos EG, Petersen RC, Boeve BF: Diagnostic utility of letter fluency, category fluency, and fluency difference scores in Alzheimer's disease. Clin Neuropsychol 2002;16:35–42.

9 Monsch AU, Bondi MW, Butters N, Salmon DP, Katzman R, Thal LJ: Comparisons of verbal fluency tasks in the detection of dementia of the Alzheimer type. Arch Neurol 1992;49: 1253–1258.

10 Spaan PE, Raaijmakers JG, Jonker C: Alzheimer's disease versus normal ageing: A review of the efficiency of clinical and experimental memory measures. J Clin Exp Neuropsychol 2003;25:216–233.
11 Hodges JR, Salmon DP, Butters N: Semantic memory impairment in Alzheimer's disease: Failure of access or degraded knowledge? Neuropsychologia 1992;30:301–314.
12 Perry RJ, Hodges JR: Relationship between functional and neuropsychological performance in early Alzheimer's disease. Alzheimer Dis Assoc Disord 2000;14:1–10.
13 Albert MS, Moss MB, Tanzi R, Jones K: Preclinical prediction of AD using neuropsychological tests. J Int Neuropsychol Soc 2001;7:631–639.
14 Jacobs DM, Sano M, Dooneief G, Marder K, Bell KL, Stern Y: Neuropsychological detection and characterization of preclinical Alzheimer's disease. Neurology 1995;45:957–962.
15 Perry RJ, Hodges JR: Fate of patients with questionable (very mild) Alzheimer's disease: Longitudinal profiles of individual subjects' decline. Dement Geriatr Cogn Disord 2000;11:342–349.
16 Hejl A, Hogh P, Waldemar G: Potentially reversible conditions in 1,000 consecutive memory clinic patients. J Neurol Neurosurg Psychiatry 2002;73:390–394.
17 McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM: Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–944.
18 American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, ed 4. Washington, American Psychiatric Association, 1994.
19 Petersen RC, Doody R, Kurz A, Mohs RC, Morris JC, Rabins PV, Ritchie K, Rossor M, Thal L, Winblad B: Current concepts in mild cognitive impairment. Arch Neurol 2001;58:1985–1992.
20 Waldemar G, Bruhn P, Schmidt E, Kristensen M, Lassen NA, Paulson OB: Cognitive profiles and regional cerebral blood flow patterns in dementia of the Alzheimer type. Eur J Neurol 1994;1:81–89.
21 Strub RL, Black FW: The Mental Status Examination in Neurology, ed 3. Philadelphia, Davis, 1993.
22 Hodges JR, Patterson K: Is semantic memory consistently impaired early in the course of Alzheimer's disease? Neuroanatomical and diagnostic implications. Neuropsychologia 1995;33:441–459.
23 Chertkow H, Bub D: Semantic memory loss in dementia of Alzheimer's type. What do various measures measure? Brain 1990;113:397–417.
24 Nebes RD: Semantic memory in Alzheimer's disease. Psychol Bull 1989;106:377–394.
25 Nebes RD, Brady CB: Preserved organisation of semantic attributes in Alzheimer's disease. Psychol Aging 1990;5:574–579.
26 Laatu S, Portin R, Revonsuo A, Tuisku S, Rinne J: Knowledge of concept meanings in Alzheimer's disease. Cortex 1997;33:27–45.
27 Caine D, Hodges JR: Heterogeneity of semantic and visuospatial deficits in early Alzheimer's disease. Neuropsychology 2001;15:155–164.
28 Berent S, Giordani B, Foster N, Minoshima S, Lajiness O-R, Koeppe R, Kuhl DE: Neuropsychological function and cerebral glucose utilization in isolated memory impairment and Alzheimer's disease. J Psychiatr Res 1999;33:7–16.
29 Hanninen T, Hallikainen M, Koivisto K, Partanen K, Laakso MP, Riekkinen PJ Sr, Soininen H: Decline of frontal lobe functions in subjects with age-associated memory impairment. Neurology 1997;48:148–153.
30 Caccappolo-Van Vliet E, Manly J, Ming-Xin T, Marder K, Bell K, Stern Y: The neuropsychological profiles of mild Alzheimer's disease and questionable dementia as compared to age-related cognitive decline. J Int Neuropsychol Soc 2003;9:720–732.
31 Hirono N, Mori E, Ishii K, Imamura T, Tanimukai S, Kazui H, Hashimoto M, Takatsuki Y, Kitagaki H, Sasaki M: Neuronal substrates for semantic memory: A positron emission tomography study in Alzheimer's disease. Dement Geriatr Cogn Disord 2001;12:15–21.
32 Hodges JR, Patterson K: Nonfluent progressive aphasia and semantic dementia: A comparative neuropsychological study. J Int Neuropsychol Soc 1996;2:511–524.
33 Pietrini V, Nertempi P, Vaglia A, Revello MG, Pinna V, Ferro Milone F: Recovery from herpes simplex encephalitis: Selective impairment of specific semantic categories with neuroradiological correlation. J Neurol Neurosurg Psychiatry 1988;51:1284–1293.
34 Wilson BA: Semantic memory impairments following non-progressive brain injury: A study of four cases. Brain Inj 1997;11:259–269.
35 Delacourte A, David JP, Sergeant N, Buee L, Wattez A, Vermersch P, Ghozali F, Fallet Bianco C, Pasquier F, Lebert F, Petit H, Di Menza C: The biochemical pathway of neurofibrillary degeneration in aging and Alzheimer's disease. Neurology 1999;52:1158–1165.